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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,936	12/12/2003	Wonchul Suh	CL1878USNA	2510
23906 7590 06/14/2007 E I DU PONT DE NEMOURS AND COMPANY LEGAL PATENT RECORDS CENTER BARLEY MILL PLAZA 25/1128 4417 LANCASTER PIKE WILMINGTON, DE 19805			EXAMINER MCGILLEM, LAURA L	
			ART UNIT 1636	PAPER NUMBER
			MAIL DATE 06/14/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	Application No. 10/734,936	Applicant(s) SUH, WONCHUL	
	Examiner Laura McGillem	Art Unit 1636	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 18 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: \_\_\_\_\_.  
 Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
 13. ☒ Other: See Continuation Sheet.

Continuation of 11. does NOT place the application in condition for allowance because: The amendment to claim 23 raises the issue of indefinite claim language. Claim 23 has been amended to depend on claim 17, and recites the phrase "said regulatory circuit", but claim 17 does not recite the limitation of a regulatory circuit. Therefore it is not clear to what regulatory circuit the limitation refers and claim 23 is vague and indefinite.

Claims 1, 3, 7-11, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (Application Publication No. 2002/0151058, of record) in view of Yu et al (of record) and further in view of Prideaux et al (U.S. Patent No. 6,472,183).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 5/25/2006) and for reasons outlined below. Applicants submit that in order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2143.

Additionally, Applicants submit that Perkins is an inappropriate reference under 35 USC § 103 and therefore, not supported. The Applicant respectfully asserts that the skilled artisan would not consider the exemplified teachings of the Perkins et al reference as relevant to the claimed invention. The Applicant provides the following reasons as to why the Perkins et al. reference should not be considered as an analogous or enabling reference suitable for supporting the Examiner's case of prima facie obviousness because the Examiner has taken excerpts from the Perkins et al. reference to form a prima facie obviousness rejection ex post facto.

Applicant submits that the Perkins et al reference is not an enabling reference nor should it be considered a valid reference and is not analogous to the claimed invention. Applicant submits that when one of ordinary skill in the art examines the teachings of the Perkins et al reference in detail, it is clear that one of ordinary skill in the art would not consider the reference as relevant to the claimed invention.

The Applicant submits that the Perkins et al reference illustrates homologous recombination using linear, double stranded DNA molecules (linearized plasmids) in a eukaryotic host cell (yeast). All of the working examples are in a eukaryotic host cell (yeast). The mechanisms of double strand break GAP-repair mediated homologous recombination in yeast is well-known in the art and is non-analogous (both structurally and functionally) to the lambda-Red recombination system. Applicant respectfully asserts that one of ordinary skill in the art would not consider a reference that only exemplifies GAP-repair mediated homologous recombination in eukaryotic cells (for the purpose of creating eukaryotic expression vector) as relevant to the lambda-Red mediated chromosomal engineering in a prokaryotic cell. Applicant respectfully asserts that one of ordinary skill in the art would not have considered nor looked towards the Perkins et al reference at the time the claimed invention was made to obtain the claimed invention.

Applicant submits the following elements that would direct one of ordinary skill in the art away from considering the Perkins et al. reference in any way relevant to the claimed method in a prokaryotic cell (*E. coli*) using lambda-Red mediated homologous recombination:

1. Applicant submits that prokaryotic and eukaryotic recombination systems are vastly different. All of the working examples in the Perkins et al. reference are based on a yeast cell model using GRIPP (gap repair with an inverse PCR-amplified plasmid). Applicant submits that GRIPP technology is dependent upon the endogenous GAP repair system. No prokaryotic host cells are exemplified or sufficiently described as to enable one of ordinary skill in the art to conclude that the exemplified process (double strand break GAP repair mediated eukaryotic plasmid synthesis) is in any way relevant to the claimed process or method in the instant application. Applicant submits that eukaryotic meiotic recombination involves a complex set of proteins often referred to as the RAD52 epistasis group and the number of proteins involved, as well as the structure of the proteins, is vastly different when compared to the lambda-Red recombination system.

2. Applicant submits that it is well known that linearized plasmids can be used for in vivo transformation in a eukaryotic cell (yeast). The endogenous double strand break (DSB) gap repair mechanism in yeast will efficiently restore double strand breaks via homologous recombination. Homologous transformation using yeast GAP repair involves numerous gene products that are not functional in *E. coli* and are structurally different to the elements of the lambda-Red recombination system.

3. Applicant submits that no working examples nor an enabling description is provided showing that the process illustrated by the Perkins et al reference is applicable to a prokaryotic system nor is there any reference to lambda-Red mediated chromosomal engineering.

4. Applicant submits that all of the examples in the Perkins et al. reference illustrate the use of GRIPP that relies on the endogenous GAP repair system in yeast to prepare eukaryotic expression plasmids only. The Applicant respectfully asserts the different end use, as well as the difference in the elements involved in eukaryotic double strand break repair further supports the assertion that the skilled artisan would not consider this reference as relevant to the claimed method.

5. Applicant submits that biotechnology is considered an unpredictable art, even when using structurally homologous elements. The differences in cellular organization and intracellular environment between eukaryotic and prokaryotic organisms, the differences in the structures of the elements involved in homologous recombination, as well as the unpredictable nature of the art, would not lead one of ordinary skill in the art to consider the Perkins et al reference as a whole, to be an appropriate and enabling reference that one could look towards to derive the claimed invention.

Given all of the significant differences between the Perkins et al. system and the claimed method in the instant application, one ordinary of skill in the art would not believe that the system taught by the Perkins et al. reference would have any reasonable expectation of success in *E. coli*, especially for a different intended purpose (i.e. multi-fragment chromosomal engineering).

Applicant's arguments filed 5/18/2007 have been fully considered but they are not persuasive. Applicant's arguments appear to be based on the submission that the Perkins reference is about homologous recombination using linearized plasmids in a yeast and is nonanalogous to the lambda-Red recombination system, therefore the skilled artisan would not have looked toward Perkins et al as a prior art reference.

In response to applicant's argument that Perkins et al is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was

concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Perkins et al teach a method to make an expression vector using triple homologous recombination in which an expression vector intermediate and a target nucleic acid are introduced into a recombination competent host. Perkins et al disclose an embodiment in which the recombination competent host cell is a recombination competent strain of *E. coli*. (see paragraph 0010). Perkins et al disclose that the DNA fragments can be in linear or circular form (see paragraph 0034, for example). Therefore, Perkins et al disclose and contemplate a method of multiple homologous recombination in an *E. coli* host cell and is analogous art.

1. In response to the submission that prokaryotic and eukaryotic recombination systems are vastly different, Perkins et al disclose an embodiment in which the recombination competent host cell is a recombination competent strain of *E. coli*. (see paragraph 0010). Therefore, Perkins et al contemplate both prokaryotic and eukaryotic recombination for a method of triple homologous recombination to integrate DNA into a chromosome.

2. Although Applicant submits that homologous transformation using yeast GAP repair involves numerous gene products that are not functional in *E. coli* and are structurally different to the elements of the lambda-Red recombination system, the GRIPP disclosure is merely an exemplification of the methods taught by Perkins et al (see Examples 1-2). Since Perkins et al disclose an embodiment in which the recombination competent host cell is a recombination competent strain of *E. coli* (see paragraph 0010), the teaching of Perkins et al can be combined with the teaching of Yu et al and Prideaux et al in order to render obvious the claimed method as detailed in Office Action mailed 5/25/2006 (pages 3-9).

3. Although Applicant submits that no working examples nor an enabling description is provided showing that the process illustrated by the Perkins et al reference is applicable to a prokaryotic system nor is there any reference to lambda-Red mediated chromosomal engineering, it is not necessary for Perkins et al to provide a working example because Perkins et al contemplates performing the method in a recombination competent strain of *E. coli*.

Furthermore, it is not the teachings of Perkins et al alone that is being used to make an obviousness rejection of the instantly claimed method, but it is the combination of Perkins et al, in view of Yu et al, and further in view of Prideaux et al. It is not necessary for Perkins et al to provide a working example of an obvious variation of the disclosed method. It would have been obvious to one of ordinary skill in the art to modify the method of Perkins et al to include the use of the recombination system taught by Yu et al because Yu et al teach it is difficult to recombine linear DNA fragments into *E. coli* genomes and that this system is an improvement over the art at the time the invention was made. The motivation to use the lambda-Red recombination system is the expected benefit as exemplified by Yu et al of being able to recombine PCR-generated linear DNA constructs comprising very short regions of homology into the *E. coli* genome in an efficient manner without additional steps that had been required using methods previously used in the art (see page 5982, right column, 1st and 2nd paragraphs, in particular). There is a reasonable expectation of success in using the lambda-Red recombination system because it has worked previously for Yu et al.

4. Applicant submits that all of the examples in the Perkins et al. reference illustrate the use of GRIPP that relies on the endogenous GAP repair system in yeast to prepare eukaryotic expression plasmids only. The Applicant respectfully asserts the different end use, as well as the difference in the elements involved in eukaryotic double strand break repair further supports the assertion that the skilled artisan would not consider this reference as relevant to the claimed method. Although Applicant submits that Perkins et al teaches a method to make only eukaryotic expression plasmids, a construct is still being made that would result in gene expression. Perkins et al disclose an embodiment in which the recombination competent host cell is a recombination competent strain of *E. coli* (see paragraph 0010). The outcome of the instantly claimed method is a bacterial chromosome with an integrated expressible DNA fragment that would be able to express the DNA fragment. Contrary to the submission of the Applicant, the end use is the same, that is, expression of DNA, whether in a eukaryotic (as exemplified by Perkins et al) or prokaryotic host (as contemplated and disclosed by Perkins et al).

5. In response to Applicant's submission that the Perkins et al reference is not an enabling reference to use in this obviousness rejection, lack of enablement must be shown by a full Wands analysis of the Forman factors: nature and scope of the invention, state of the art, unpredictability of the art, amount of guidance, amount of working example and level of skill in the art. Applicant has not fully demonstrated lack of enablement of the combination of the teaching of Perkins et al, in view of Yu et al, and further in view of Prideaux et al.

Claims 1, 3-4, 7-8, 11, 13-17, 20-22 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (Application Publication No. 2002/0151058, of record) in view of Yu et al (of record) and further in view of Welch et al (Application Publication No. 2002/0187544) as evidenced by Guzman, et al (J. Bacteriol., 1995, 177(14): 4121-4130).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 5/25/2006) and for reasons outlined below. Applicants reiterate that Perkins does not make the present invention obvious in as much as the skilled person would have no motivation to combine Perkins with Yu or Welch and would have no reasonable expectation of success as argued above.

Applicant's arguments filed 5/18/2007 have been fully considered but they are not persuasive. Applicant's argument regarding Perkins et al has been addressed above. Applicants do not provide other arguments specific to the combination of Perkins et al and Yu et al further in view of Welch et al as evidenced by Guzman et al.

#### Continuation of 13. Other:

Once a final rejection that is not premature has been entered in an application, applicant or patent owner no longer has any right to unrestricted further prosecution. For reasons given above, and on the grounds that the amended claims raise further issues for consideration, the amended claims have not been entered. The amendments do not place the application either in condition for allowance or in better form for appeal. Applicant is invited to review MPEP 714.12.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571)272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


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you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD  
Examiner  
6/5/2007

CELINE QIAN, PH.D.  
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'C. Qian', written over a horizontal line.